HIV-1 Drug Resistance at Low- and High-Level Viremia in Kenyan Youth on Dolutegravir-Based Therapy

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Vlad Novitsky[1], Winstone Nyandiko[2,3], Joel Hague[1], Allison DeLong[1], Edwin Sang[2], Ashley Chory[4,5], Josephine Aluoch[2], Eslyne Jepkemboi[2], Millicent Orido[2], Joseph Hogan[1,2], Rachel Vreeman[4,5], **Rami Kantor**[1]

[1] Brown University, Providence, RI, USA; [2] Academic Model Providing Access to Healthcare (AMPATH), Eldoret, Kenya; [3] Moi University, Eldoret, Kenya; [4] Icahn School of Medicine at Mount Sinai, New York, NY, USA; [5] Arnhold Institute for Global Health, New York, NY, USA

BACKGROUND

Understanding of the extent and patterns of HIV-1 drug resistance in the era of globally widespread dolutegravir therapy is limited, particularly for youth. Drug resistance data on low-level viremia (LLV; 200-1,000 copies/mL) are sparse, primarily due to technical difficulties with genotyping at low RNA levels, and the evolving global definitions of treatment failure.

METHODS

We developed a protocol for LLV genotyping by next generation sequencing (NGS), applied it to Kenyan youth with perinatal HIV, who were longitudinally followed for four years (2020-2024), and had viral non-suppression (viral load >40 copies/mL) on dolutegravir-based regimens. We compared the extent of NRTI, NNRTI and INSTI resistance between specimens with LLV and those with high-level viremia (HLV; viral load >1000 copies/mL; current WHO threshold). Established drug resistance mutations (DRMs) were defined by the Stanford Database at NGS frequency ≥20%, while minority drug resistance variants were considered at frequency 2-20%. Differences in proportions were estimated using Fisher's exact test.

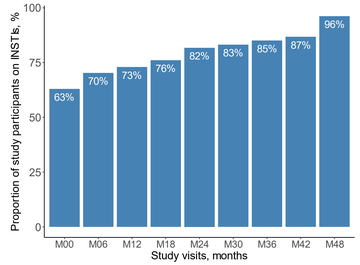


Figure 1. Study participants on INSTI-based regimens

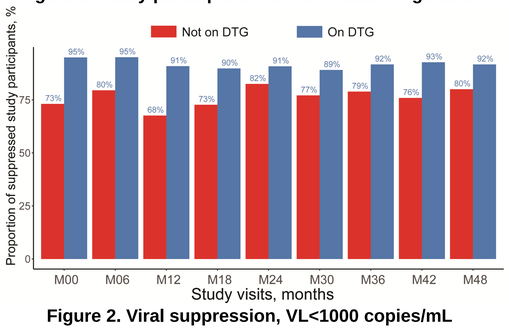


Figure 2. Viral suppression, VL<1000 copies/mL

In Kenyan youth with perinatal HIV failing dolutegravir-based regimens, newly developed genotyping protocol for low-level viremia resistance testing revealed similar overall and class-specific resistance proportions in low-level compared to high-level viremia, including INSTI minority resistance variants.

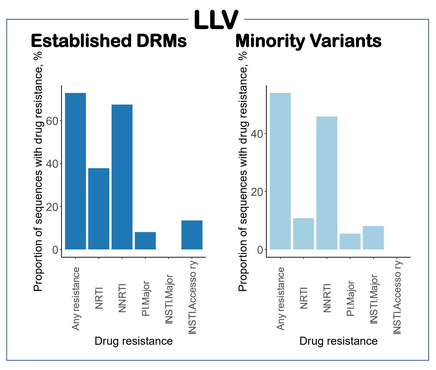
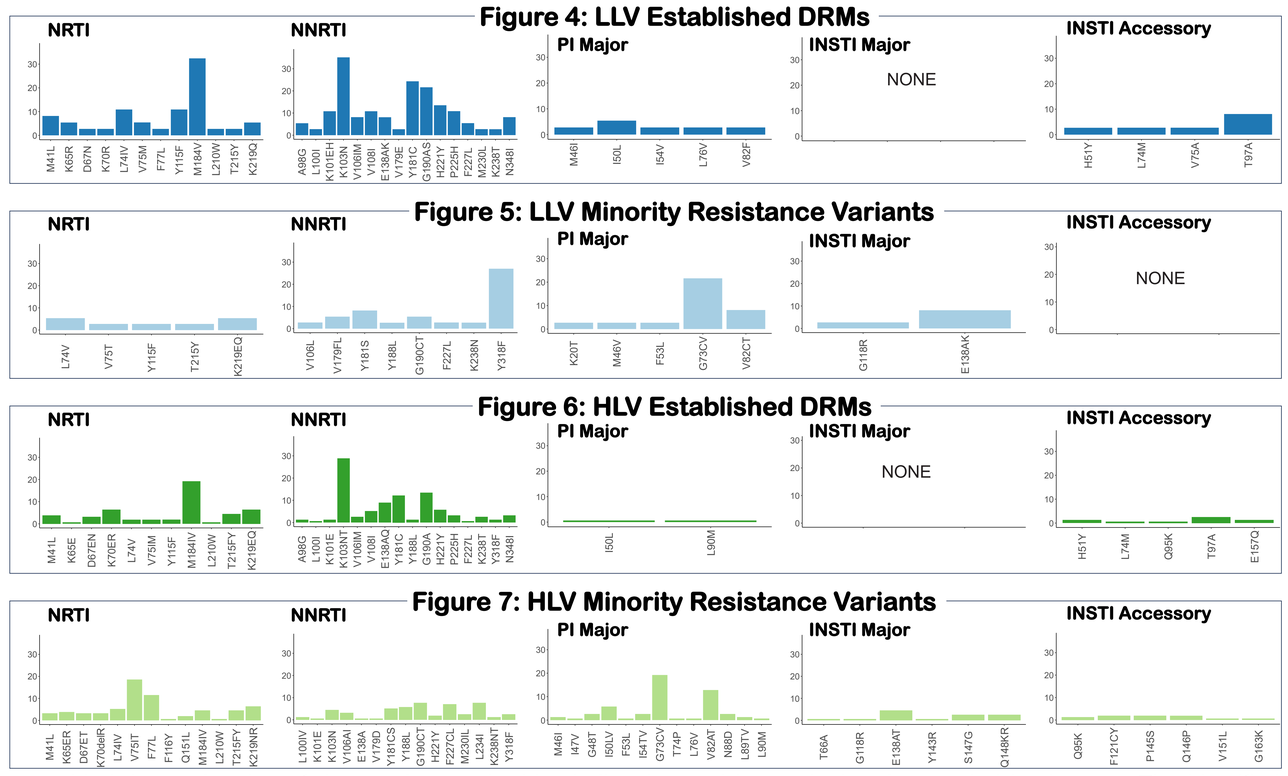


Figure 3. LLV and HLV drug resistance by antiretroviral class: established DRMs vs. minority resistance variants.

RESULTS

In 446 participants (median age 21 years; 49% female; median 15 years on antiretroviral therapy), the proportion on dolutegravir-based regimens gradually increased from 63% to 96% over 48 months (Figure 1). The median proportion of virally suppressed participants was 92% (range 89%-95%) for those on dolutegravir, and 77% (range 68%-83%) for those not on dolutegravir (Figure 2). Among participants on dolutegravir-based regimens, established DRMs to any antiretroviral class were found in 73% of LLV sequences and 55% of HLV sequences, while minority resistance variants were detected in 54% of LLV sequences and 61% of HLV sequences (Figure 3). Figures 4-7 demonstrate established DRMs and minority resistance variants for LLV and HLV, most of which were overall at similar proportions.



CONCLUSIONS

Developing a genotyping protocol for LLV has enabled the exploration of drug resistance in this challenging and increasingly relevant viral load range. The identified treatment failure in this vulnerable Kenyan youth population on dolutegravir-based regimens, along with the observed overall similar resistance prevalence in LLV versus HLV, is concerning, especially with the presence of major INSTI minority resistance variants. Longitudinal follow-up to determine the impact of these findings is ongoing.